Complete Summary

GUIDELINE TITLE

Evidence based clinical practice guideline for pneumocystis carinii pneumonia prophylaxis following solid organ or blood and marrow transplants.

BIBLIOGRAPHIC SOURCE(S)

Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for pneumocystis carinii pneumonia prophylaxis following solid organ or blood and marrow transplants. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2001 Jan 12. 9 p. [80 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Pneumocystis carinii pneumonia following solid organ or blood and marrow transplants

GUIDELINE CATEGORY

Evaluation
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Critical Care
Gastroenterology
Hematology

Infectious Diseases
Internal Medicine
Nephrology
Pediatrics
Pulmonary Medicine

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To examine the published incidence of Pneumocystis carinii pneumonia (PCP) in patients undergoing heart, kidney, liver, or blood and marrow transplants and to develop recommendations for primary prophylaxis for these post transplant patients based on the best scientific evidence available, taking into consideration the age of the recipient, prior exposure to the pathogen, type of transplant, degree of immunosuppression, and post transplant interval

TARGET POPULATION

These guidelines are intended for use in the following types of transplant patients from 0 to 18 years of age:

- Patients receiving prophylaxis to prevent primary infection following solid organ, blood and marrow transplant (from transplantation to 6–12 months following transplantation depending on level of immunosuppression)
- Patients that experience graft rejection or Graft versus Host Disease >1 year following transplantation

These guidelines are <u>not</u> intended for use in the following types of transplantation patients:

- Patients presenting with prior history of Pneumocystis carinii pneumonia (PCP)
- Patients with Pneumocystis carinii pneumonia
- Patients requiring marked alterations in routine prophylaxis due to significant complications of illness
- Patients experiencing immunosuppression for reasons other than transplantation

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention/Treatment

1. Initiation of prophylaxis for Pneumocystis carinii pneumonia (PCP) within the first month after transplantation and continued for a minimum period of 6

months for solid organ and autologous blood and marrow transplant recipients.
2. Prophylaxis (PCP) following allogeneic blood and marrow transplantation continued for the first year
3. Reinitiation of prophylaxis for solid organ, blood and marrow transplant recipients during periods of either rejection or Graft versus Host Disease therapy because of heightened immunosuppression
4. Trimethoprim-sulfamethoxazole (TMP-SMX) used as first-line of therapy in the prophylaxis of PCP
5. Aerosolized pentamidine as an alternative prophylactic therapy in transplant recipients who have myelosuppression or who have experienced an allergic reaction to TMP-SMX
6. Dapsone as an alternative for children unable to tolerate the administration of an aerosolized treatment
7. Intravenous pentamidine for use in patients with myelosuppression or who have experienced adverse reactions with either TMP-SMX or dapsone
8. Atovaquone prophylaxis (might rarely be considered for prophylaxis when no other regimen is tolerated)

Clinical Surveillance and Laboratory Assessments for PCP

1. Monitoring for hypoxemia and changes on chest radiograph if tachypnea, dyspnea, or cough develops
2. Obtaining fluid or tissue from the lower respiratory tract by bronchoscopy or bronchoalveolar lavage (BAL) for pathologic evaluation from patients who are suspected to have PCP
3. Utilizing Grocott's Methenamine Silver (GMS) staining when a bronchoalveolar lavage specimen is obtained (Note: polymerase chain reaction [PCR] and fluorescent antibody techniques are considered but not recommended for PCP diagnosis)

MAJOR OUTCOMES CONSIDERED

- Effectiveness of prophylactic regimens in preventing Pneumocystis carinii infection
- Sensitivity and specificity of laboratory screening tests for Pneumocystis carinii

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature search was conducted utilizing the Medline, Embase, and Cochrane Databases. Search strategies were focused on answering pertinent clinical questions using Medical Subject Headings (MeSH) and searching on words in the title, abstract, and indexing terms. The number of citations was then reduced by

eliminating duplications and non-English articles. Articles were subset by pediatric or adult subjects.

Further searches were performed as additional queries arose. Members were also requested to present important abstracts and presentations from scientific meetings that pertained to the guideline issues.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The guideline team read, graded and summarized the evidence.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The recommendations contained in this document were formulated by a multidisciplinary team that included community and hospital based physicians and specialists, nurses, respiratory therapists, and others, as appropriate, who examined current local clinical practices and performed an extensive literature search and critical literature review. Articles were reviewed and scored using a grading scale.

Members were also requested to present important abstracts and presentations from scientific meetings that pertained to the guideline issues. From the total review of evidence found, the team developed the guideline recommendation statements.

During formulation of these guidelines, the team members remained cognizant of controversies and disagreements over the management of these patients. They tried to resolve controversial issues where possible and, when not possible, to

offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines have been reviewed and approved by senior management, Legal Services, the Institutional Review Board, the hospital's Pharmacy and Therapeutics, Clinical Practices, Executive, and other committees and other individuals as appropriate to their intended purposes.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each recommendation is followed by evidence grades (A-X) identifying the type of supporting evidence. Definitions of the evidence grades are presented at the end of the "Major Recommendations" field.

Prophylaxis

1. It is recommended that the initiation of prophylaxis be considered within the first month after transplantation and continued for a minimum period of 6 months for solid organ (Gordon et al., 1999 [D]; Fishman & Rubin, 1998 [S]; Rubin et al., 1981 [S]) and autologous blood and marrow transplant recipients (Dykewicz, Kaplan, & Jaffe, 1999; Centers for Disease Control and Prevention [CDC], 1997 [E]). It is recommended that prophylaxis for Pneumocystis carinii pneumonia (PCP) following allogeneic blood and marrow transplantation be continued for the first year (Vasconcelles et al., 2000 [D]; Dykewicz, Kaplan, & Jaffe, 1999; CDC, 1997 [E]).
2. It is recommended that, in addition to the initial prophylaxis period, reinitiation of prophylaxis be considered for solid organ and blood and marrow transplant recipients during periods of either rejection or Graft versus Host Disease therapy because of heightened immunosuppression (Gordon et al., 1999 [D]; Kramer et al., 1992 [D]).
3. It is recommended that trimethoprim-sulfamethoxazole (TMP-SMX) be considered as first-line therapy in the prophylaxis of PCP in these transplant recipient populations. TMP-SMX has been demonstrated in studies to be more

efficacious than either dapsone or aerosolized pentamidine, although many of these studies have been completed in the human immunodeficiency virus (HIV) patient population (Ioannidis et al., 1996 [M], Dykewicz, Kaplan, & Jaffe, 1999; CDC, 1997 [E], Vasconcelles et al., 2000 [D]). The recommended dose of TMP-SMX is 5 mg/kg/day (based on the trimethoprim component, maximum daily dose 320 mg) given on a thrice-weekly schedule, such as Monday – Wednesday – Friday, or on three consecutive days per week (see Table 2 in the original guideline document).

Note 1: TMP-SMX has been shown to prevent PCP in solid organ, blood and marrow transplant recipients (Olsen et al., 1993 [B]; Kramer et al., 1992 [D]; Elinder et al. 1992 [D]; Gordon et al., 1999 [D]; Hughes et al., 1987 [B]; Torre-Cisnernos et al., 1996 [C]) and when given three times per week, toxicity is decreased (Ioannidis, 1996 [M]; Bozzette et al., "The tolerance for zidovudine," 1995 [B]).

Note 2: In addition to preventing PCP, TMP-SMX may also prevent nocardia and toxoplasmosis infections (Gordon et al., 1999 [D]; Fishman & Rubin, 1998 [S]).

4. It is recommended that aerosolized pentamidine be considered as alternative prophylactic therapy in transplant recipients who have myelosuppression or who have experienced an allergic reaction to TMP-SMX (Saukkonen, Garland, & Koziel, 1996 [D]; Link et al., 1993 [C]) for children six years of age or older. For the purpose of these guidelines, myelosuppression is defined as an absolute neutrophil count <1,000. Another alternative may be dapsone for children >1 month to six years who may be unable to tolerate the administration of an aerosolized treatment (Dykewicz, Kaplan, & Jaffe 1999 [ ]; CDC, 1997 [E]; Maltezou et al., 1997 [D]) (see Table 2 in the original guideline document).

   Note: Dapsone and aerosolized pentamidine have been shown to be equally efficacious for the prevention of PCP (Ioannides et al., 1996 [M]; Slavin et al., 1992 [B]. However, the risk for severe side effects is four fold greater with dapsone than with pentamidine (Ioannides et al., 1996 [M]). The adverse effects with dapsone are not shown as different when compared to TMP-SMX (Ioannidis et al., 1996 [M]; Mallolas et al., 1993 [B]; Vasconcelles et al., 2000 [D]). Dapsone is less expensive compared to aerosolized pentamidine.

5. It is recommended that intravenous pentamidine be considered for use in patients with myelosuppression (absolute neutrophil count [ANC] <1,000) or who have experienced adverse reactions with either TMP-SMX or dapsone (Gupta et al., 1997 [O]; Lidman et al., 1993 [D]). Effective dosing may not be achieved with aerosolized pentamidine in children <6 years of age (Hand et al., 1994 [C]). (see Table 2 in the original guideline document.)

   Note: Severe adverse effects from the use of intravenous pentamidine for PCP prophylaxis are uncommon. Mild adverse effects are primarily infusion related (e.g., rash pruritis). More significant adverse effects, including hypoglycemia and pancreatitis, have been reported with daily intravenous use but are rare with prophylactic use (Lidman et al., 1993 [D]; Gupta et al., 1997 [O]).

6. If all recommended regimens are not tolerated, atovaquone might rarely be considered for prophylaxis.

   Note: Although atovaquone has been shown to be effective in the prophylaxis of PCP in adolescent and adult human immunodeficiency virus (HIV) population (El-Sadr et al., 1998 [A]), there is little known of its use in children (Hughes, 1998 [S]).

7. It is recognized that randomized trials of PCP prophylaxis have not been conducted against current immunosuppression therapies. However, it remains local expert opinion that prophylaxis for PCP still be considered following solid organ or blood and marrow transplant (Local Expert Consensus [E]).

Clinical Surveillance for PCP

1. It is recommended that recipients of solid organ, blood and marrow transplants at risk for PCP be monitored for hypoxemia and changes on chest radiograph if tachypnea, dyspnea, or cough develop, regardless of the presence or absence of other findings (Janner et al., 1996 [D]; Fishman & Rubin, 1998 [S]).

   Note 1: Oxygen saturations <90% or chest radiograph findings consistent with PCP may indicate reason for suspicion of Pneumocystis carinii (Janner et al., 1996 [D]; Olson et al., 1993 [B]).

   Note 2: Individuals with confirmed PCP often have abnormal findings on chest radiograph (Egan et al., 1996 [D]; Fishman & Rubin, 1998 [S]); only 3.5% of confirmed cases of PCP are associated with normal chest radiographs (Gordon et al., 1999 [D]).

   Note 3: Radiographic findings associated with PCP may vary widely. They may be alveolar or interstitial in nature, and most often they are diffuse, bilateral, symmetric, and reticular in appearance. However, atypical patterns may include isolated lobar disease, focal parenchymal lesions, cavitary or miliary patterns, endobronchial lesions, or pleural effusions (Kuhlman, 1996 [S]).

   Note 4: Fever and/or auscultory findings of pneumonia may be minimal (Janner et al., 1996 [D]; Gordon et al., 1999 [D]).

Laboratory Assessment for PCP

1. It is recommended that individuals who are suspected to have PCP have tissue or fluid obtained from the lower respiratory tract for pathologic evaluation. Bronchoscopy with bronchoalveolar lavage (BAL) should be strongly considered, as children frequently cannot expectorate true lower respiratory specimens.

   Note 1: The diagnostic sensitivity is greater for BAL (95–100%) (von Eiff et al., 1995 [D]; Fraser et al., 1996, [C]) than for sputum specimens (50–60%)

(Metersky, Aslenzadeh, & Stelmach, 1998 [D]); therefore, a sputum negative for P. carinii does not rule out the diagnosis of PCP.

Note 2: Transbronchial lung biopsy does not significantly increase the diagnostic sensitivity for PCP (Fraser et al., 1996 [C]); however, open lung biopsy may be required in 1 to 5% of cases (Yale & Limper, 1996 [D]; Thomas & Limper, 1998 [S]).

2. It is recommended that Grocott's Methenamine Silver (GMS) staining be utilized when a BAL specimen is obtained.

   Note 1: GMS staining of BAL specimens is associated with 97% sensitivity for PCP diagnosis (Baughman et al., 1989 [C]). (See Table 3 in the original guideline document.)

   Note 2: In contrast to polymerase chain reaction (PCR) (investigational) or fluorescent antibody staining, GMS may also be more clinically useful by detecting etiologic agents other than Pneumocystis, including yeasts, pseudohyphae, and true hyphae. In some cases, even bacteria can be visualized with the GMS stain. In addition, routine staining provides a more rapid response time as compared to polymerase chain reaction testing (Armbruster, Pokieser, & Hassl, 1995 [C]; Sing et al., 2000 [C]).

Definitions:

Evidence Based Grading Scale:

A: Randomized controlled trial: large sample
B: Randomized controlled trial: small sample
C: Prospective trial or large case series
D: Retrospective analysis
E: Expert opinion or consensus
F: Basic laboratory research
S: Review article
M: Meta-analysis
Q: Decision analysis
L: Legal requirement
O: Other evidence
X: No evidence

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is identified and classified for each recommendation (see "Major Recommendations") using the following scheme:

Evidence Based Grading Scale:

A: Randomized controlled trial: large sample
B: Randomized controlled trial: small sample
C: Prospective trial or large case series
D: Retrospective analysis
E: Expert opinion or consensus
F: Basic laboratory research
S: Review article
M: Meta-analysis
Q: Decision analysis
L: Legal requirement
O: Other evidence
X: No evidence

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Decrease morbidity
- Decrease mortality
- Trimethoprim-sulfamethoxazole (TMP-SMX) may also prevent nocardia and toxoplasmosis infections.
- Dapsone is less expensive compared to aerosolized pentamidine.

POTENTIAL HARMS

- Risk for severe side effects is four fold greater with dapsone than with pentamidine.
- Mild adverse effects using intravenous pentamidine for Pneumocystis carinii pneumonia (PCP) prophylaxis are primarily infusion related (e.g., rash pruritis)
- More significant adverse effects using intravenous pentamidine for PCP include hypoglycemia and pancreatitis with daily intravenous use but are rare with prophylactic use.

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindication for use of trimethoprim-sulfamethoxazole (TMP-SMX) or dapsone:

Patients with myelosuppression or who have experienced adverse reactions

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The recommendations of this evidence based clinical practice guideline address prophylaxis and not treatment options. Pneumocystis carinii pneumonia (PCP) is diagnosed by identifying trophozoites, cyst walls, or nuclear components from the organism in tissue or fluid obtained from the lower respiratory tract of an individual with clinical and/or radiographic respiratory disease. This is an indication to discontinue prophylaxis and begin a therapeutic regimen.
- These recommendations result from review of literature and practices current at the time of their formulations. This protocol does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the guidelines to meet the specific and unique requirements of individual patients. Adherence to these recommendations is voluntary. The physician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The implementation process for each Cincinnati Children's Hospital Medical Center (CCHMC) guideline is a phase in a larger process of Guideline Development. This process is utilized for every guideline but is not addressed in the content of every guideline.

At the start of each guideline, a projected implementation date is determined. Reservations for education are then made (Grand Rounds, Patient Services Inservices). When the guideline is complete and enters into the Approval Process, education planning begins. Changes created by the guideline are outlined as well as anticipated outcomes. The implementation date is confirmed. Education is provided. The guideline is implemented and pilot information collection started. The Guideline Coordinator makes daily rounds and eligible children are followed to document the use of the guideline. The implementation phase aids in finding areas for improvement or question. When issues identified are improved, the guideline progresses to the monitoring phase

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Jan 12

GUIDELINE DEVELOPER(S)

Cincinnati Children's Hospital Medical Center - Hospital/Medical Center

SOURCE(S) OF FUNDING

Cincinnati Children's Hospital Medical Center

GUIDELINE COMMITTEE

Clinical Effectiveness Team for Pneumocystis Carinii Pneumonia (PCP)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Infection Prophylaxis – PCP Clinical Effectiveness Team Members 2000: Brett Loechelt, MD (Blood & Marrow); James Acton, MD (Pulmonology); John Bucuvales, MD (Liver); Beverly Connelly, MD (Infectious Disease); Stephen Guthery, MD (Fellow); Robert Spicer, MD (Heart); Paul Steele, MD (Pathology); Fred Strife, MD (Kidney); David Witte, MD (Pathology); Stavra Xanthakos, MD (Chief Resident)

Patient Services: Tamara Hutson, PharmD (Pharmacy); Joyce Slusher, RN (Transplant Coordinator); Rhonda Struck, RN (T5A Director); Karen Uzark, PhD, CPNP (Heart Center); Carla Wallace, PharmD (Pharmacy)

Clinical Effectiveness Services: Mary Pat Alfaro, RD, MS; Betsy Bushman, BA; Wendy Gerhardt, RN, MSN; Uma Kotagal, MBBS, MSc; Anna Russell, BA; Kate Turck, BS

Ad Hoc Advisors: William Balistreri, MD (Gastroenterology/Nutrition); Jeff Pearl, MD (Cardiology/Cardiovascular Surgery); Melissa Berner, ESQ (Legal Services);

Michael Farrell, MD (Chief of Staff); Thomas Gross, MD (Blood and Marrow Transplant); Kathy Latta, RN (Education Services); Irwin Light, MD (Institutional Review Board); Dorine Seaquist, RN, MS (VP, Patient Services); Beth Stautberg, ESQ (Legal Services); Alan Brody, MD (Radiology)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cincinnati Children's Hospital Medical Center Web site.

For information regarding the full-text guideline, print copies, or evidence based practice support services contact the Children's Hospital Medical Center Health Policy and Clinical Effectiveness Department at HPCEInfo@chmcc.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on March 11, 2004.

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